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Research Article

Tuberculosis Incidence and All-Cause Mortality among Human Immunodeficiency Virus-Infected Patients on Isoniazid Preventive Therapy in Dar Es Salaam, Tanzania

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Abstract

Objective: We determined rates of tuberculosis (TB) incidence and all-cause mortality among patients who received Isoniazid preventive therapy (IPT) for 6 months and among a control group that did not receive IPT.

Methods: A prospective cohort study was conducted among 2564 HIV-infected patients in Dar-es-Salaam, Tanzania between February 2012 and March 2014. The Tanzania National Tuberculosis and Leprosy Program clinical screening tool was used to exclude active TB before enrollment into the study. Patients were followed up for a total of 24 months. Multivariate Cox proportional hazards were used for analysis and results are presented as adjusted relative hazard (aHR) and 95% confidence intervals (CI).

Results: TB incidence was 91 cases/100,000 person-years (PY) (95% CI 11-328) in patients who received IPT and 511 cases/100,000 PY (95% CI 255-915) in control group. There was 79% reduction in TB risk among patients receiving IPT (aHR=0.21, 95% CI 0.25-1.77, p=0.15) after adjusting for use and duration of antiretroviral (ARV) and current CD4 T cell counts. All-cause mortality rate was 136 deaths/100,000 PY (95% CI 28-398) and 1115 deaths/100,000 PY (95% CI 715-1659) in IPT and the control groups, respectively. There was an 83% reduction in the risk of death among patients receiving IPT (aHR=0.17, 95% CI 0.64-0.74, p=0.02) after adjusting for use and duration of ARV and current CD4 T cell counts.

Conclusion: IPT does not significantly reduce the risk of TB but that of all-cause mortality in HIV-infected patients whose majority were already on ARV medication.

Keywords: Tuberculosis incidence; Isoniazid preventive therapy; Clinical screening; HIV infection; All-cause mortality

Abbreviations

aHR: adjusted Hazard ratio; AIDS: Acquired Immunodeficiency Syndrome; ARV: Antiretroviral Drugs; CD4: Cluster+D6:D28 of Differentiataion 4; CI: Confidence Interval; CTC: Care and Treatment Centre; GIT: Gastrointestinal Truct; HIV: Human Immunodeficiency Virus; INH: Isoniazid; IPT: Isoniazid Preventive Therapy; IQR: Interquartile Range; LJ: Lowenstein-Jensen culture media; LTBI: Latent Tuberculosis Infection; MDG: Millenium Development Goal; MNH: Muhimbili National Hospital; MUHAS: Muhimbili University of Health and Allied Sciences; NTLP: National Tuberculosis and Leprosy Programme; PASADA: Pastoral Activities and Services for People with AIDS in Dar es Salaam; PY: Person years; SD: Standard deviation; TB: Tuberculosis; TST: Tuberculin Skin Test; UNAIDS: Joint United Programme for Human immunodeficiency virus and acquired immunodeficiency syndrome; WHO: World Health Organization; ZN: Ziehl-Nielsen stain

Introduction

Tuberculosis (TB) continues to be the leading cause of morbidity and mortality among HIV-infected individuals. This happens in the midst of global celebration of achieving the 2015 Millennium Development Goal number 6 (MDG 6) of halting and reversing TB incidence [1]. In the year 2013 there were 9.0 million new TB cases and 1.5 million TB deaths; 0.4 million deaths estimated to have occurred among HIV-infected patients [1]. Reducing TB incidence among HIV-infected patients is therefore crucial in ensuring sustained achievement of MDG 6. Previous studies have shown that treatment of latent tuberculosis infection (LTBI) in HIV-infected patients regardless of drug type, frequency or duration of treatment is associated with a greater reduction of the risk for active TB when compared to placebo [2,3]. A systematic review by Bucher et al, 1999 found that isoniazid (INH) chemoprophylaxis reduced the risk of active TB by 42% among HIV-infected patients, with further 60% reduction among those with positive tuberculin skin test (TST) [3]. Another systematic review by Akolo et al., 2010 found a risk reduction by 32% for the development of active TB among patients on TB preventive therapy compared to placebo. A more pronounced reduction of the risk for active TB by 68% was seen in patients with a positive TST [2].

Based on the findings of early studies on INH preventive therapy

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(IPT) among HIV-infected patients, in the year 1998 the World Health Organization (WHO) and the Joint United Programme for HIV and Acquired Immunodeficiency Syndrome (UNAIDS) recommended IPT as part of the comprehensive HIV and AIDS care strategy [4]. However, by the end of 2009, only 85,000 HIV-infected patients were on IPT globally. Small numbers of patients being put on IPT globally are mainly due to economic reasons, especially in developing countries, and lack of an acceptable approach to exclude active TB [4]. It was therefore recommended by WHO that adults living with HIV should be screened for TB with a clinical algorithm and that eligible patients be initiated on IPT [4].

Reported TB incidences in patients on TB preventive therapy are variable among studies. In the Swiss HIV cohort study, screening for LTBI was done using TST and none of the 193 patients screened and who received either isoniazid, rifabutin combined with pyrazinamide, rifabutin alone, rifampicin combined with pyrazinamide or rifampicin alone, presented with active TB during the study follow up period [5]. In a Kenyan study, patients were screened using TST and the incidence of TB was 4.29 per 100 person years (PY) in the IPT group and 3.86 per 100 PY in the placebo group. From this study it was concluded that there was no statistically significant protection from TB following administration of daily INH for 6 months [6]. A study in Zambia with similar screening methodology had 96 TB incident cases among 1053 study participants [7].

TB preventive therapy is known to have little (if any) advantage on all-cause mortality among HIV-infected patients. Bucher et al, 1999 and Akolo et al, 2010 did not find any advantage of TB preventive therapy over placebo or no TB preventive therapy on mortality [2,3]. One previous study in South Africa however found significant reduction of the risk for early mortality by 49% among patients on ART who received IPT compared to those who did not receive IPT after adjusting for age, baseline CD4 T cell count, baseline WHO HIV disease stage, year of start of ARV and individual company [8]. The present study was conducted to determine the rates of TB incidence and all-cause mortality among HIV-infected patients who were initiated on IPT after a clinical screening using a Tanzania National Tuberculosis and Leprosy Program (NTLP) symptom-based TB screening tool whose sensitivity and specificity in detecting active TB has been described elsewhere [9]. We have previously demonstrated an overall IPT mean adherence (±SD) of 98.9 (±2.9) [10].

Methods

Study design, site and population

A prospective cohort study was conducted at six urban-based clinics providing HIV/AIDS treatment services in Dar es Salaam between February 2012 and March 2014. These clinics were situated at the Muhimbili National Hospital (MNH), a referral tertiary hospital which is also a teaching hospital for the Muhimbili University of Health and Allied Sciences (MUHAS) as well as the clinics that served at secondary level of care (Mwananyamala, Amana and Temeke municipal hospitals). Other facilities were healthcare centers at Buguruni and Pastoral Activities and Services for people with AIDS in Dar es Salaam Archdiocese (PASADA). All the health facilities except MNH served as primary level care facilities for HIV/AIDS. The MNH clinic provided primary level care as well as management of HIV treatment failures. HIV treatment failures from the rest of the facilities were managed at a higher-level referral clinic in Dar es Salaam that was not included in this study. The clinics at MNH, Amana, Temeke and PASADA were among the fourteen centers participating in a separate pilot IPT program that assessed the feasibility of a nationwide provision of IPT to HIV infected patients. We used the National IPT pilot program as an opportunity window to conduct the present study. Patients from these four clinics were invited to participate in the study and constituted an IPT group. Patients from Mwananyamala and Buguruni facilities were not part of the national IPT pilot program and were thus enrolled to form a control group.

The HIV clinics operate five days a week and each clinic attends approximately 70-100 patients daily. All HIV-infected patients are seen monthly for clinical evaluation and receiving refills of ARV drugs.

Data collection procedures

Trained Nurses and Doctors informed patients about the present study that went along with the national IPT pilot program and invited them to participate. Eligible patients were aged 10 years or older, HIV-infected outpatients, ARV naïve or experienced and were willing to stay in Dar es Salaam for at least 2 years. Exclusion criteria included known alcohol abuse, a current or past history of hepatitis or other medical contraindications to IPT. Additional exclusion criteria were current or recent (within the past two years) TB treatment, pregnancy, a history of treatment non-compliance or the presence of WHO HIV clinical stage 4 AIDS [11]. Informed consent was obtained from each participant prior to enrolment in the study. Children provided assent and their guardians provided a signed consent.

Patients underwent screening to exclude active TB using the National Tuberculosis and Leprosy Program (NTLP) symptom-based screening tool [12]. The tool is comprised of 5 questions asking for the presence of cough for ≥ 2 weeks, fever for ≥ 2 weeks, hemoptysis of any duration, excessive night sweats for ≥ 2 weeks and noticeable weight loss or weight loss of ≥ 3 kg within 4 weeks. We previously demonstrated that the screening tool had 71.4% sensitivity and 75.9% specificity for identifying active TB in an HIV positive population being considered for IPT. The positive and negative predictive values of the screening tool were 11.4 and 98.4%, respectively, with a false negative rate of 28.6% [9].

Patients who presented with none of the symptoms in the screening tool were considered not to have active TB and were assessed for IPT eligibility as described above. Patients who presented with any of the symptoms in the screening tool were designated as being active TB suspects and underwent standard TB screening. These were enrolled in the study once active TB was excluded. Screening procedures as well as the inclusion and exclusion criteria were the same for the IPT and the control groups.

Eligible patients were consecutively enrolled into the study and initiated on IPT if they attended one of the 4 clinics at MNH, Temeke, Amana and PASADA. Patients from Mwananyamala and Buguruni did not receive IPT. For both treatment groups, we collected baseline socio-demographic and clinical data. Patients in the IPT group were provided with a monthly supply of 30 tablets of INH 300 mg to be taken orally daily for a total of 6 months. Patients in the two

groups were followed up for a total of 24 months. At each monthly visit the TB screening survey tool was repeated for the two groups to identify those who could have possibly developed active TB during the follow up period. Clinical history was collected at each monthly visit to identify any new clinical developments, or drug side effects for the patients on IPT. A thorough examination of the respiratory system, lymphatic system, skin and mucous membranes, as well as gastrointestinal tract (GIT), cardiovascular, central nervous and musculoskeletal systems for any concurrent illness was conducted at each visit. We also recorded weight to the nearest 0.5 kg using an analogue scale (SECA), patients being on light clothing. Temperature was measured in degrees Celsius using a digital thermometer. Patients who screened positive to the NTLP screening tool were provided with two 50 mL falcon tubes for sputum collection. The 1st specimen of sputum was collected on the spot in an open air and the patient was instructed to collect a 2nd specimen in the morning of the following day. Sputum samples were then transported on the same day to a TB laboratory located at the Infectious Diseases Control (IDC) center in the city for Mycobacterium tuberculosis Ziehl-Nielsen (ZN) staining (smear microscopy) and culture in Lowenstein–Jensen (LJ) media. All smear negative individuals underwent a chest X-ray examination.

Definition of terms

TB was defined according to the NTLP definition which requires the presence of two of the following: (i) Symptoms of TB (cough, fever, night sweats, loss of weight for more than 2 weeks), (ii) AFB visible by direct Ziehl-Nielsen staining of sputum specimen or M. tuberculosis cultured from sputum in Lowenstein–Jensen media, (iii) Chest radiograph independently interpreted as highly suggestive of TB (iv) TB in organs other than the lungs proven by one culture positive specimen from an extra-pulmonary site or histopathological evidence from a biopsy OR a strong clinical evidence, including macroscopic evidence of specimen inspection, consistent with active extra-pulmonary TB and the decision by a medical doctor to treat with a full course of anti-tuberculous therapy (v) a clinical response to anti-TB medication in patients with culture- negative TB [11].

All-cause mortality was defined as death from any cause occurring after recruitment into the study. Patients missing 2 consecutive visits were tracked to their residences to ascertain causes of not attending the clinic. Deaths that occurred at home were documented. However no verbal autopsies were done.

Lost to follow up was defined as absence from the clinic for two consecutive scheduled visits and efforts to track the patients were in vain.

Baseline CD4+ cell counts referred to CD4+ cell counts which were taken within 6 or less months of enrollment into the study.

Transferred out patients were patients who shifted from a care and treatment (CTC) clinic of enrollment to the study to another CTC which was not among the study sites.

Study end points

Primary end points were; a diagnosis of active TB during follow up, all-cause mortality, lost to follow up and transfer out. Secondary end point was death from TB defined as death occurring in a patient diagnosed with TB that was not related to any form of accident.

Ethical issues

Ethical clearance for the study was obtained from MUHAS Senate Research and Publications Committee (Reference number MU/DRP/AEC/Vol. XVI/135). All the involved healthcare facilities granted permission to conduct the study. All patients gave a written informed consent. Patients aged < 18 years assented to the study and had their parents/guardians consent on their behalf. Patients who screened positive to the tool were fully worked up to diagnose or exclude active TB. Following the diagnosis of active TB, patients were initiated on a full course of anti-TB treatment as per Tanzania guidelines [11]. Patients' data were handled with high confidentiality.

Statistical analysis

Assuming a TB incidence during IPT of 3.4% from Bakari et al., 2011[13] and a 2.8% rate of TB suspects using the symptom based TB screening tool (From pilot study) we calculated the sample size to be 1031 participants per group (IPT group and Controls) at 5% significance and a statistical power of 80%. Considering an attrition rate of 20%, we aimed at recruiting 1289 patients in each group.

Data were analyzed using SPSS version 20.0. Baseline characteristics were analyzed using proportions and medians ± interquartile range (IQR) and means (± SD). Chi square was used to compare proportions, student t-test to compare means while medians were compared using K independent samples. TB incidence was estimated by dividing the total number of TB cases by total person years of follow up. Kaplan-Meier plots were used to estimate TB-free and mortality-free survival probabilities. TB-free survival was defined as the time from enrolment to the date of TB diagnosis or the last follow-up visit. Mortality-free survival was defined as the time from enrollment to the date of death from any cause or the last follow-up visit. We used a log-rank test to compare TB-free and mortality-free survival probabilities between the IPT group and the control group, and $p<0.05$ was regarded as significant. Cox proportional hazard regression models were fitted to determine predictors for TB and all-cause mortality. Variables were considered for inclusion in the multivariate model if they were found associated with the risk of TB or all-cause mortality at $p <0.2$.

Results

A total of 2564 HIV-infected patients were enrolled in the study. Of these, 1283 patients were for the IPT group and 1281 patients were for the control group. At enrollment, the overall median age (interquartile range [IQR]) for all the patients was 38 (32-45) years. The median age was 39 (33-46) years among patients on IPT and 37 (31-43) years among the controls, ($p< 0.001$). Baseline (CD4+ cell count at enrollment) median CD4 T cell count for all patients was 317 cells/μL [interquartile range (IQR) 306 cells/μL]. Baseline CD4 T cell count (IQR) for IPT group was 367 (233-553) cells/μL. Median baseline CD4 T cell count (IQR) was 279 (172-447) cells/μL for the control group, $p<0.001$.

The majority of patients on IPT were older than in the control group (52.7% vs 42.9%, $p<0.001$), had some form of employment (86.5% vs 78.9%, $p<0.001$), had HIV disease for more than 2 years since diagnosis (93.4% vs 90.1%, $p=0.005$), were using ARV drugs (76.5% vs 72.7%, $p=0.025$), were on ARV treatment for more than 2 years (92.2% vs 84.6%, $p<0.001$) and had CD4 T cell counts >350

Table 1: Socio-demographic and clinical characteristics of the patients at enrollment.

Characteristic	All patients N=2564	IPT group N=1283	Control group N=1281	P value
	Number (%)	Number (%)	Number (%)	
Sex: Males	615 (24.0)	289 (22.5)	326(25.4)	
Females	1949 (76.0)	994(77.4)	955(74.6)	0.083
Age in years: ≤ 38	1338(52.2)	607(47.3)	731(57.1)	
>38	1226(47.8)	676(52.7)	550(42.9)	<0.001
Education *N=812				
Primary level or less	614 (75.6)	311 (74.9)	301(76.3)	
Secondary or post-secondary	198 (24.4)	104 (25.1)	94(23.7)	0.646
Occupation: Jobless	455(17.7)	185(14.4)	270(21.1)	
Working	2109(82.3)	1098(85.6)	1011(78.9)	<0.001
Socioeconomic status: Low	1031(40.2)	521(40.6)	510(39.8)	
Medium and High	1533(59.8)	762(59.4)	771(60.2)	0.681
BMI in kg/ m^2 (adults only), *N=2366				
< 18.5	299(12.6)	146(12.4)	153(12.9)	
≥18.5	2067(87.4)	1034(87.6)	1033(87.1)	0.699
HIV duration in years, *N=2229				
≤ 2	185 (8.3)	72 (6.6)	113(9.9)	
> 2	2044(91.7)	1014(93.4)	1030(90.1)	0.005
ARV use: Yes	1913	982(76.5)	931(72.7)	
No	651	301(23.5)	350(27.3)	0.025
ARV duration in years, *N=1893				
≤ 2	219(11.6)	74(7.8)	145(15.4)	
> 2	1674(88.4)	876(92.2)	798(84.6)	<0.001
Current CD4+ count (cells/µl), *N=2357				
< 350	1292(54.8)	582(47.0)	710(63.5)	
≥350	1065(45.2)	657(53.0)	408(36.5)	<0.001

*Number may not add to total due to missing covariates.

Table 2: Distribution of study outcomes at the end of 24 months of follow up, N=2564.

Study outcome	Total	Patients on IPT, N=1283	Controls N=1281	P value
	Number (%)	Number (%)	Number (%)	
Active TB*	13 (1.1)	2 (0.2)	11(0.9)	0.012
All-cause mortality	27(0.5)	3(0.2)	24(1.9)	<0.001
Lost to follow up	146(5.7)	73(5.7)	73 (5.7)	0.992
Transferred out	110(4.3)	31(2.4)	79(6.2)	<0.001
Withdrawal of consent	13(0.5)	10(0.8)	3(0.2)	0.052
Pregnant*	21(0.8)	2(0.2)	19(1.5)	<0.001
Completed study	2268(88.5)	1166(90.9)	1102(86.0)	<0.001

*Patients were followed to the end of the study.

cells/µL (52.9% vs 36.2%, p< 0.001) (Table 1).

The 2-year follow- up period resulted into a total follow up period of 4357 person years of observations (PY), 2205 PY in the IPT group and 2152 PY in the control group. The mean (± SD) follow up time was 1.7 (0.4) years. The rate of loss to follow up was similar in the two groups, being 73 (5.7%) patients in each group. Transferred out patients were 31 (2.4%) among IPT cases and 79 (6.2%) in the control group. More 10 (0.8%) patients in the IPT group withdrew consent to continue with the study than were in the control group, 3 (0.2%) patients. Two (0.2%) patients in the IPT group became pregnant and had to stop IPT while 19 (1.5%) patients in the control group became pregnant (Table 2).

During the 2-year follow-up period, a total of 13/2564 patients were diagnosed with TB, giving an incidence rate of 298 (95% CI

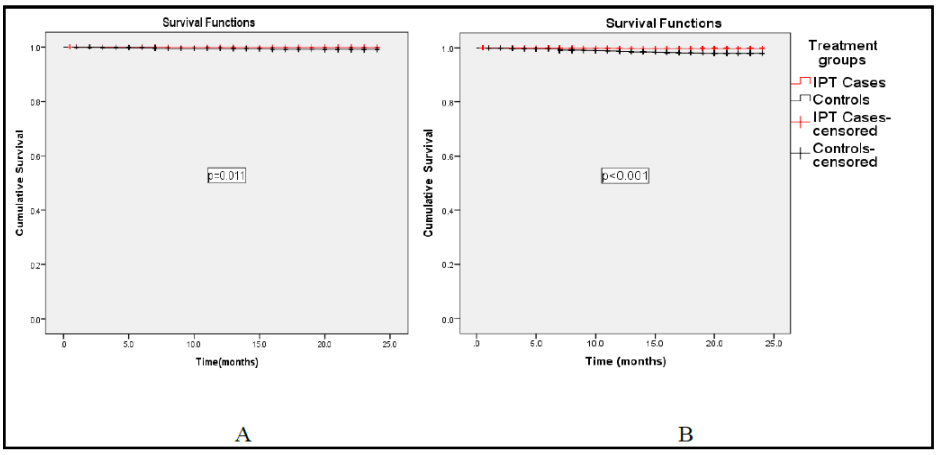

Figure 1: (A). Cumulative survival from incident tuberculosis, (B). Cumulative survival from all-cause mortality.

Table 3: Cox regression analyses of predictors of Tuberculosis among the study population; N=2564.

Variable	Number with TB/ Total*	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Sex: Male	3/615	1			
Female	10/1949	1.04(0.29-3.79)	0.949		
Age in years					
≤ 38	9/1338	1			
>38	4/1227	0.48(0.15-1.55)	0.219		
Education level					
Primary or lower	3/614	1			
Secondary or higher	2/198	2.1(0.35-12.55)	0.417		
Occupation					
Jobless	4/455	1			
Working	9/2109	0.48(0.15-1.55)	0.21		
SES					
Low	3/1031	1			
Medium & high	10/1533	2.23(0.61-8.10)	0.223		
HIV duration (years)					
0-2	2/185	1			
>2	11/2044	0.50(0.11-2.23)	0.35		
ARV use					
Yes	7/1913	1		1	
No	6/651	2.59(0.87-7.7)	0.087	No estimate	
ARV duration (years)					
0-2	3/219	1		1	
>2	4/1674	0.17(0.04-0.76)	0.02	0.23(0.05-1.07)	0.06
Current CD4 (cells/µl)					
<350	9/1292	1		1	
≥350	1/1065	0.13(0.02-1.05)	0.055	0.40(0.05- .77)	0.406
IPT treatment					
No	2/1283	1		1	
Yes	11/1281	0.18(0.04-0.80)	0.025	0.21(0.25-1.77)	0.15

*Number may not sum to total due to missing covariates.

Table 4: Cox regression analyses of predictors of all-cause mortality among the study population, N=2564.

Variable	Number died/ Total*	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Sex: Male	9/615	1			
Female	18/1949	0.63(0.28-1.39)	0.249		
Age in years					
≤ 38	16/1338	1			
>38	11/1226	0.74(0.34-1.59)	0.441		
Education level					
Primary or lower	6/614	1			
Secondary or higher	2/198	1.06(0.21-5.23)	0.948		
Occupation					
Jobless	5/455	1			
Working	22/2109	0.93(0.35-2.46)	0.886		
SES					
Low	11/1031	1			
Medium & high	16/1533	0.98(0.45-2.10)	0.948		
HIV duration (years)					
0-2	2/185	1			
>2	23/2044	1.03(0.24-4.38)	0.965		
ARV use					
Yes	17/1913	1		1	
No	10/651	1.78(0.81-3.88)	0.149	1.60(0.21-12.19)	0.649
ARV duration (years)					
0-2	7/219	1		1	
>2	11/1674	0.2(0.08-0.51)	0.001	0.27(0.10-0.77)	0.014
Current CD4 (cells/µl)					
<350	15/1292	1		1	
≥350	5/1065	0.4(0.14-1.10)	0.074	0.81(0.25-2.58)	0.712
IPT treatment					
Yes	3/1283	0.12(0.04-0.41)		0.17(0.04-0.74)	
No	24/1281	1	0.001	1	0.02

*Number may not sum to total due to missing covariates.

159-510) cases per 100,000 PY. In the IPT group 2/1283 patients developed TB, giving an incidence rate of 91 (95% CI 11-328) cases per 100,000 PY. On the other hand, 11/1281patients developed TB in the control group, giving an incidence rate of 511 (95% CI 255-915) cases per 100,000 PY.

During the 2-year period of follow-up a total of 27 patients died, giving an overall all-cause mortality rate of 620 (95% CI 408-908) deaths/100,000 PY. There were 3 deaths in the IPT group, giving an all-cause mortality rate of 136 (95% CI 28-398) deaths/100,000 PY, and 24 deaths in the control group, giving an all-cause mortality rate of 1115 (95% CI 715-1659) deaths /100,000 PY, p<0.001.

Patients who received IPT significantly showed longer survival from TB disease than the control group (p=0.011), and significantly longer survival from all-cause mortality than the control group, p<0.001 (Figure 1).

Table 3 shows the various predictors of incident TB among the study population. In a univariate analysis, patients who received IPT had an 82% decreased risk for developing TB compared to those who did not receive IPT (HR = 0.18, 95%CI 0.04-0.80, p=0.025). Furthermore, patients who used ARV for two years or longer had an 83% decreased risk for TB compared to those who used ARV for less than two years (HR = 0.17, 95% CI 0.04-0.76, p=0.020). Also, patients with current CD4 T cell counts of 350 cells/µL or more had an 87% decreased risk for TB compared to patients with current CD4 T cell counts of <350 cells/µL with marginal significance (HR= 0.13, 95% CI 0.02-1.05, p=0.055). There was no association between incident TB and variables like sex, age, education level, occupation, SES and HIV duration.

In multivariate analysis neither IPT, ARV use status, nor current CD4 T cell counts could predict development of active TB. However, patients on ARV for more than 2 years had a 77% decreased risk for developing TB compared to patients who used ARV for 2 years or less (HR= 0.23, 95% CI 0.05-1.07, p=0.06).

Autopsies were not done to ascertain causes of death, however there were 2 deaths among TB patients. Table 4 shows predictors of all-cause mortality among the study population. In a univariate analysis patients who received IPT were found to have an 88% decreased risk for all-cause mortality compared to patients who did not receive IPT (HR 0.12, 95% CI 0.04-0.41, p=0.001). Similarly, patients who had used ARV for more than two years had a 98% decreased risk for all-cause mortality as compared to patients who used ARV for less than two years (HR 0.2, 95% CI 0.08-0.51, p=0.001). However, all-cause mortality was not associated with gender, age, education level, occupation, socio-economic status, and duration of HIV infection since diagnosis, ARV use status, or current CD4 T cell counts.

In multivariate analysis, patients who received IPT had an 83% decreased risk for all-cause mortality compared to patients who did not receive IPT after adjusting for ARV use status, duration of ARV use and current CD4 T cell counts (HR0.17, 95% CI 0.04-0.74, p= 0.018). Patients who used ARV for more than two years had a 73% decreased risk for all-cause mortality compared to those who used ARV for two years or less after adjusting for ARV use status, current CD4 T cell counts, and IPT use status (HR 0.27, 95% CI 0.10-0.77, p=0.014). Neither ARV use duration nor current CD4 T cell counts could predict all-cause mortality.

Discussion

The present study assessed the rates of TB incidence and all-cause mortality among HIV infected patients who received Isoniazid for six months as TB preventive therapy. Rates of TB incidence and all-cause mortality were compared to rates among patients who did not use IPT. The overall TB incidence was 298 cases per 100,000 PY which is far higher than the 164 cases per 100,000 PY incidence of TB among the general population of Tanzania [14]. This finding signifies that TB still poses greater burden of disease among HIV infected patients. In the present study, multivariate Cox proportional hazards modeling revealed a 79% decreased risk for TB among patients who were on IPT. This association however was not statistically significant. Lack of significance can partly be explained by the fact that majority (about 75%) of the patients in the present study were already on ARV treatment for HIV. ARV alone was found to reduce TB incidence by more than 80% when compared to no ARV in one study in South Africa, an area endemic for both tuberculosis and HIV-1 [15]. Lack of significance can also be partly explained by fewer TB incident cases in both groups. A randomized study in Nairobi Kenya found no statistically significant protective effect of daily isoniazid for 6 months in the prevention of tuberculosis [6]. Lack of significance in the Nairobi study was discussed to be possibly due to a small sample. Other studies however, have demonstrated the benefit of Isoniazid in reducing the risk for TB. The risk for TB was reduced by 76% among patients receiving both ART and IPT in Rio de Janeiro, Brazil [16]. Similarly, a study in Port-au-Prince, Haiti demonstrated TB risk reduction among patients who received Isoniazid and pyridoxine compared to those who received pyridoxine alone [17]. International union against tuberculosis committee on prophylaxis demonstrated different levels of TB risk reduction when Isoniazid was given to patients with pulmonary fibrotic lesions compatible with TB for 12, 24 or 52 weeks. It was not stated whether the patients were on HAART or not [18]. On the other hand, a cluster randomized trial of IPT among 78,744 miners in South Africa did not establish any significant reduction of the cluster level TB incidence or mortality during the 12 months follow up post intervention period among those who received IPT compared to those who did not [19]. However, HIV serostatus of the South African miners was unknown. In the present study, patients on ARV for longer than 2 years showed a 77% decreased risk for tuberculosis compared to patients who used ARV for 2 years or less. This finding is possibly explained by the fact that ARV treatment preserves the immunity and thus improves the ability to fight tuberculosis and other infections [20,21]. Immune preservation is dependent on the duration of effective use of ARV.

Adjusting for ARV use status, duration of ARV use and current CD4 cell counts, patients who received IPT showed significant reduction of the risk for all-cause mortality as compared to patients who did not receive IPT. This finding is contrary to the findings by Akolo et al., 2010 [2] and those by Quigley et al 2001[22] who found no difference in the risks for death between those who received TB preventive therapy and those who did not receive TB preventive therapy. In the two studies [2,22] it was not stated whether the study population were on antiretroviral therapy or not. Given the fact that the studies were done in 1990s and early 2000s when ARV use was to very few patients who could afford the cost of medication, there is no doubt that majority of the participants in the 2 studies were not on ARV. If this is the case then the findings of the present study (whose three quarters of its subjects were on ARV) may suggest that mortality benefit from IPT is largely among patients who are already on ARV treatment for more than 2 years.

We could not ascertain the cause of deaths to many patients, however, there is a possibility that some of the deceased patients had died of undiagnosed tuberculosis. This notion may further explain the significant reduction of the risk for all-cause mortality among those who received IPT. Furthermore, there is a possibility that those who received IPT not only benefitted from the anti-tuberculous effect of INH but also from the antibacterial effect of INH metabolites. This is evidenced by an in vitro antibacterial effect against Staphylococcus aureus ATCC 9144 and Escherichia coli ATCC 11303 of a new ligand derived by the condensation of INH metabolite isonicotinoylhydrazide and 3-ethoxysalicylaldehyde [23].

Study Strengths and Limitations

The strengths of this study are a large sample size, prospective cohort design and low loss to follow up. However, no autopsies were done to ascertain causes of death. Some deaths might have occurred from undiagnosed TB. Furthermore, the two groups were incomparable at baseline; therefore the interpretations of the findings of the present study should take this difference into consideration.

Conclusion

IPT does not significantly reduce the incidence of tuberculosis in HIV-infected patients on ARV therapy for more than 2 years. However, IPT significantly reduced all-cause mortality. IPT provision can therefore be used to reduce all- cause mortality, which might be due to undiagnosed tuberculosis in HIV infected patients.

Authors' Contributions

GAS, CM, SA, MB and FM designed the study. GAS supervised

data collection and data management. GAS and CM analyzed the data. GAS prepared the 1st draft of the manuscript. All the authors participated in manuscript preparation and approved the final manuscript for publications.

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